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Description

The present invention is related to pharmaceutical extended release preparations of active compounds with very low solubility, especially substituted dihydropyridines, and to methods of preparing such preparations.

The object of this invention is to obtain a solid preparation with high extent of bioavailability and extended release of an active compound which normally has very low solubility.

Pharmaceuticals with very poor water solubility present formulation problems due to their slow rate of dissolution. Their efficacy can be severely limited and large interindividual variations of absorption can occur. Examples of drugs with very low solubility are some substituted dihydropyridine compounds such as nifedipine and felodipine. The mentioned dihydropyridines are commonly classified as calcium antagonists, which are widely used for the treatment of cardiovascular disorders such as ischaemic heart disease and arterial hypertension. One of the mentioned dihydropyridines, namely felodipine, has a solubility of only 0.5 mg/l in water. Other examples of drugs with very low solubility are griseofulvin, digoxin, oxazepam, phenytoin and cyclosporine.

Several ways to increase drug absorption have been described in the prior literature. One way is described in DE-A-3O24858, where a sparingly soluble substituted dihydropyridine, nicardipine, is used in its amorphous form in order to obtain increased absorption of the active compound from the intestine. Another way is described in EP-A-47899, where very small crystals of a practically insoluble dihydropyridine, nifedipine, have been used in order to increase the extent of the bioavailability. These methods and others are also described in "Techniques of solubilization of drugs", Ed S.H. Yalkowsky in Drugs and the pharmaceutical sciences, Vol. I2. Of particular relevance to the present invention is that surfactant solubilizing agents may be employed in order to increase the bioavailability of the drugs with very low solubility. It is stated that the improvement of absorption properties can be ascribed to three processes: (I) increased wetting, (2) increased permeability of membranes and (3) solubilization. The cited publication describes several examples and serves as a good review of the state of the art concerning the solubilizing of drugs, especially in order to increase the bioavailability of drugs with very low solubility.

From DE-A-34OOlO6 controlled release preparations are known containing one or more natural,partially synthetic or synthetic polymers, one or more lipophilic and/or hydrophilic solvents or thickeners together with one or more pharmaceutically active compounds. In the examples it is described to use a solubilizer in an amount by weight to the active compound which is much less than I:I.

In the medical treatment of various diseases, e.g. in the cardiovascular, gastrointestinal and chemotherapeutic field, it is an advantage to have a constant concentration of the administered drug in the blood. Thus an extended release of the drug from the pharmaceutical preparation is wanted.

It is important that the extended release preparation delivers the amount of drug needed to maintain an adequate and even effect during the entire therapeutic dosage interval. This usually means that the drug should be delivered at a constant rate to give an even concentration of administered drug in the blood. This is of specific importance for drugs having a small therapeutic index, that is a small difference between effective and toxic concentration. A delayed and constant release of the drug will also be of importance for locally irritating drugs having potential risk of causing gastrointestinal disturbances when present in large local concentrations or for drugs having a short elimination half-life. In the latter case a less frequent administration and thus better patient compliance (cf. Hayes R.B. et al. Clin.Pharm.Ther. (1977), 22, p. 125-130) may be obtained with extended release preparations compared with conventional dosage forms.

Chemical Abstracts, Vol. 104, 1986, 17466y, Columbus , Ohio, USA, refers to controlled release of nifedipine in tablet form the tablets consisting of two kinds of granules, namely nifedipine + surfactant and nifedipine + a polymer, eg 2-hydroxypropyl methyl cellulose phthalate. According to said document it is thus necessary to use two kinds of granules in order to obtain a controlled release as the first kind of granules give a rapid release and the second an extended release.

Chemical Abstracts, Vol.99, 1983, No 128360d, Columbus, Ohio, USA, refers to nifedipine formulations prepared by adding alcohol to a mixture containing nifedipine and stearic acid polyoxyl-40, spraying said mixture on granules consisting of lactose and microcrystalline cellulose and transferring said granules into tablets.

Chemical Abstracts, Vol. 92, 1980, No 135278s, Columbus, Ohio Chemical Abstracts, Vol. 77, 1972, No 39130g ; and Chemical Abstracts, Vol. 70, 1969, No 17133p disclose that the solubility and the dissolution of certain drugs, eg. griseofulvin, increases with increasing concentrations of certain non-ionic surfactants in the dissolution medium.

Chemical Abstracts, Vol. 92, 1980, No 82429h, Columbus, Ohio refers to a solution of nifedipine, glycerine and/or propylene glycol and polyoxyethylated castor oil filled into soft capsules.

A drug in extended release form is generally given via the oral route. The preparations should preferably give an extended and reproducible release of drug and contribute to a reproducible absorption, have no toxic or irritating constituents and be suitable also for high dosage drugs. Conventionally, extended release is achieved by controlling dissolution and/or diffusion of medicament from the dosage form. Several materials are employed for this purpose e.g. waxes, fatty materials, polymers, natural, synthetic and semisynthetic gums. Among the gums, hydroxypropyl methylcellulose (HPMC) constitutes an important class because of its pH-independent properties as well as its semisynthetic origin. A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms is given by Alderman D.A. Int.J.Pharm.Tech.&Prod.Mfr (I984), 5(3) I-9. The chemical treatment of HPMC to generâte a desired constitution and the use of these qualities are disclosed in US 3 O87 79O, US 4 226 849, US 4 357 469 and US 4 369 I72. SE-A-8OO8646-5 describes a combination of HPMC and hydroxypropyl cellulose which is used to control the release rate of a pharmaceutically active compound.

When a hydrophilic matrix issued the soluble polymer forms a gelatinous layer around the tablet after the exposure of the tablet to gastro-intestinal fluids or saliva. The release of the drug is limited by the rate of water penetration into, and diffusion of drug through, the gel formed (Bamba et al. Int.J.Pharm. (I979), 2, 3O7). Erosion of the gel structure is also an important release mechanism of a drug from the system. The polymers used have to hydrate rapidly in order to protect the tablet from fast dissolution (Alderman I984).

The rate of absorption of a drug with very low solubility into the circulation from the intestinal tract is closely related to the rate of dissolution. Since a low dissolution rate generally results in a low extent of bioavailability it is difficult to decrease the rate of absorption, i.e. increase the duration, without at the same time lowering the extent of bioavailability.

Description of the invention

It is the object of the present invention to provide a preparation of a drug with very low solubility that shows prolonged and nearly constant rate of drug absorption for a long period of time and concurrently maintains a high extent of bioavailability. The object is reached by using a solubilizer which is mixed with the drug with very low solubility. The solubilizers suitable according to the invention are defined below. The active compound is preferably dissolved or dispersed in the solubilizer. The mixture of active compound (drug) and solubilizer can be diluted with water or intestinal juice without significant precipitation of the dissolved drug. In the solution the drug is included in a micell-structure formed by the solubilizer. With other commonly used solubilizers or co-solvents dilution may cause precipitation of the drug. The mixture of the drug and the solubilizer is incorporated into a pharmaceutical formulation, which gives prolonged release.

Drugs suitable for the extended release preparation according to the invention are compounds characterized by their very low solubility, that is less than O.I per cent by weight in water. In addition they are solubilizable in a solubilizer or in a combination of a solubilizer and water. Examples of drugs suitable according to the invention are some substituted dihydropyridines, such as nifedipine and felodipine. Felodipine is 4-(2,3-dichlorophenyl)-I,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid ethyl methyl ester. Nifedipine is I,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethylester. Felodipine and nifedipine both are practically insoluble compounds and therefore they are very suitable to solubilize. Other examples of drugs with very low solubility are griseofulvin, digoxin, oxazepam, phenytoin and cyclosporine.

The solubilizers suitable for the preparations according to the invention are semi-solid or liquid non-ionic surface active agents, especially such containing polyethyleneglycols as esters or ethers. They are preferably chosen from polyethoxylated fatty acids, hydroxylated fatty acids and fatty alcohols. It is especially preferred to choose the solubilizer from the group polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil. Commercially available solubilizers, which can be used are known under the trade names Cremophor, Myrj, Polyoxyl 40 stearate, Emerest 2675, Lipal 395 and HCO 50. A specially preferred solubilizer is Cremophor®RH 40 (BASF).

The active compound mixed with the solubiliser is incorporated into a controlled release system comprising a hydrophilic gel system. According to the invention the solubilized drug is combined with a hydrophilic gel system, namely a hydrophilic swelling matrix e.g. HPMC. This form of controlled release mechanism is a suitable way to control the release of the micelles of drug and solubilizer. The technical properties are good and also the performance in vivo is good. Among different hydrophilic materials tested, HPMC, hydroxypropyl methylcellulose, is the best gel-forming material. Other examples of suitable

compounds effecting the release of the active compound from the hydrophilic gel system are guar gum, xanthan gum, carboxypolymethylene, different cellulosic materials e.g. sodium carboxymethylcellulose and hydroxypropyl cellulose, lactose and aluminium silicate.

The preparation according to the invention contains 20-80% by weight, preferably 30-50% by weight of the hydrophilic gel system.

The major part of the hydrophilic gel system has a viscosity below 100 mPa•s (cps). It is especially preferable to use HPMC having a hydroxypropyl content of 4-12% by weight, especially about 8.5% by weight and a viscosity lower than 100 mPa•s (cps), e.g. 6,15 and/or 50 mPa•s (cps). The viscosity is measured by a standardized method described e.g. in United States Parmacopeia XXI, 1985, p. 672.

The final preparation is e.g. in the form of a gel tablet. By a careful choice of fillers and binders as well as gel forming material the preparation can be manufactured into a commercially acceptable form, e.g. a tablet or a hard gelatin capsule comprising the gel forming granulate, that shows unexpectedly good absorption of the active compound as well as a prolonged duration of action. In the preparation according to the invention the proportions between the active compound and the solubilizer varies in the range from 1:1 to 1:10, preferably in the range from 1:2 to 1:6.

Examples

The following examples illustrate the invention:

Example 1

	g
Felodipine	10
Cremophor RH 40	90
Calcium phosphate	250
Hydroxypropyl methylcellulose 2910 6 mPa•s (cps)	250
Xanthan gum	25
Guar gum	25
Sodium stearyl fumarate	13

The composition according to Example 1 was formed to hydrophilic matrix tablets containing 10 mg of felodipine/tablet. The tablets were prepared in the following way:
Felodipine was dissolved in Cremophor RH 40 and the solution obtained was carefully mixed with the carrier materials, HPMC, xanthan gum, guar gum and calcium phosphate. The mixture was granulated with ethanol and dried. Sodium stearyl fumarate was added as a lubricant and tablets were prepared by compression in a tabletting machine.

Example 2

	g
Felodipine	10
Cremophor RH 60	90
Aluminium silicate	100
Paraffin	80
Hydroxypropyl cellulose	7.4
Sodium stearyl fumarate	5.0

The composition according to Example 2 was formed to controlled release tablets, inert porous matrix type, containing 10 mg of felodipine/tablet. The tablets were prepared in the following way:
Felodipine was dissolved in Cremophor RH 60 and the solution obtained was mixed carefully with the carrier materials aluminium silicate and paraffin. The mixture was granulated with a solution of hydrox-

ypropyl cellulose in ethanol and dried. Sodium stearyl fumarate was added as a lubricant and tablets were prepared by compression in a tabletting machine. A controlled release of felodipine was achieved according to the in vitro results, 50% released after 2 hours and 100% released after 6 hours.

Example 3

	g
Felodipine	20
Cremophor RH 40	100
Polyvinylpyrrolidone	66.5
Cellulose, microcrystalline	62
Maize starch	29.5
Lactose	157
Ethylcellulose	36
Hydroxypropyl methylcellulose 2910 6 cps	12
Gelatin capsules	

The composition according to Example 3 was formed to controlled release capsules containing 20 mg of felodipine/capsule. The capsules were prepared in the following way:
Felodipine was dissolved in Cremophor and the solution obtained was mixed carefully with the carrier, polyvinylpyrrolidone, cellulose, maize starch and lactose. The mixture was moistened with water and spheronized. The granules obtained were dried and sieved, the fraction 0.71-1.12 mm was used. The cores were coated with ethylcellulose dissolved in a mixture of methylene chloride and ethanol. The coated granules were filled into hard gelatine capsules.

Example 4

	g
Felodipine	20
Myrj 51	120
Hydroxypropyl methylcellulose 2910 50 cps	200
Cellulose, microcrystalline	20
Lactose	167
Sodium stearyl fumarate	10.5

The composition according to Example 4 was formed to controlled release tablets containing 20 mg of felodipine/tablet. The tablets were prepared in the same way as described in Example 1.

Example 5

	g
Nifedipine	20
Cremophor RH 40	50
Hydroxypropyl methylcellulose 2910 50 cps	70
Hydroxypropyl methylcellulose 2910 6 cps	160
Cellulose microcrystalline	6
Lactose	56
Aluminium silicate	94
Sodium stearyl fumarate	10

The composition according to Example 5 was formed to hydrophilic matrix tablets containing 20 mg of nifedipine/tablet. The tablets were prepared in the same way as described in Example 1.

The best mode of carrying out the invention is at present considered to be Example 5.

Reference Example A

The following example illustrates the reference tablet used in in vivo studies

	g
Felodipine	25
Lactose	250
Methylcellulose	0.5
Polyvinylpyrrolidone	1.5
Magnesium stearate	3

The composition according to reference Example A was formed to fast-dissolving, conventional tablets containing 25 mg of felodipine/tablet. The tablets were prepared in the following way:
Felodipine was micronized and mixed with lactose and methylcellulose. The mixture was granulated with water and dried. Polyvinylpyrrolidone and magnesium stearate were added and the mass was compressed to tablets.

Reference Example B

	g
Felodipine	66
Methylcellulose	13
Mannitol	870
Polyvinylpyrrolidone	30
Cellulose, microcrystalline	40
Ethylcellulose N 10	34
Polyethyleneglycol 6000	41.8

The composition according to Reference Example B was formed to controlled release capsules containing 10 mg felodipine/capsule. The capsules were prepared in the following way:
Felodipine was micronized and carefully mixed with the carrier, mannitol, methylcellulose, polyvinylpyrrolidone and cellulose. The mixture was moistened with water and spheronized. The granules obtained were dried and sieved, the fraction 0.71-1.12 mm was used. The cores were coated with ethylcellulose and polyethyleneglycol dissolved in a mixture of methylene chloride and isopropyl alcohol. The coated granules were filled into hard gelatine capsules.

Biopharmaceutical studies

Felodipine

In the attached Figure 1 the average plasma values (nmol/1) for the compositions according to Example 1, 4 and Reference Example A have been illustrated. A single dose of 20 mg felodipine in a controlled release preparation according to the present invention was administered to 6 healthy male subjects. The plasma concentrations of felodipine were compared with the plasma concentrations after a single dose of a fast dissolving tablet containing 25 mg of felodipine. As can be seen the preparations according to the invention gave lower peaks in the plasma concentration whereas the fast-dissolving tablet gave an unwanted high peak.

The area under the plasma concentration curve (AUC) from time 0 to infinity was

Preparation	Dose mg	AUC/dose nmol • h^{-1} • l • mg^{-1}
Reference A	25	7.2
Example 1	20	8.8
Example 4	20	7.4

As can be seen from this table the bioavailability of felodipine was not decreased with the controlled release preparations.

In the attached Figure 2 the average plasma values (nmol/1) for the compositions according to Example 3 and Reference Example B have been illustrated. A single dose of 20 mg felodipine in a controlled release preparation according to the present invention was administered to 5 healthy male subjects. The plasma concentrations of felodipine were compared with the plasma concentrations after a single dose of a conventional controlled release preparation, that is without the solubilizer, containing 10 mg of felodipine. As can be seen the preparation according to the invention gave a low peak in the plasma concentration and a considerable extent of bioavailabillty. The Reference gave no detectable plasma concentration which clearly indicates the need of a solubilizer if a controlled release effect is wanted.

Nifedipine

In the attached Figure 3 the average plasma values (nmol/1) for the composition according to Example 5 and a reference formulation containing nifedipine, Adalat® 10 mg (Bayer) (Reference C) have been illustrated. Adalat® is a fast release preparation on the market. A single dose of 20 mg nifedipine in the controlled release preparation according the present invention was administered to 6 healthy male subjects. The plasma concentrations of nifedipine were compared with the plasma concentration after a single dose of the reference formulation containing 10 mg nifedipine. As can be seen the preparation according to the invention gave a lower peak in the plasma concentration, whereas the reference preparation gave an unwanted high peak in spite of the fact that the dose is the half. No substantial reduction in bioavailability can be seen when the Reference C was compared with Example 5.

The area under the plasma concentration curve from time 0 to infinity was:

Preparation	Dose mg	AUC/dose nmol • h^{-1} • l • mg^{-1}
Adalat®, Bayer	10	46.5
Example 5	20	36.0

Discussion

The examples above and the attached figures I, 2 and 3 illustrate the advantages of the controlled release preparation according to the invention in comparison with a conventional preparation or a controlled release preparation without solubilizer, all containing the same active compound. By the solubilization of the active compound with very low solubility it is possible to obtain a tablet having a more constant plasma concentration profile and without any unwanted high peaks. Also an effect during an extended period of time was obtained. Often there is a reduction in the extent of the bioavailability, when drugs with very low solubility are formulated. This invention provides however a technique of making controlled release preparations of drugs with very low solubility with the above-mentioned advantages and without any substantial reduction in the extent of the bioavailability.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A solid preparation with extended release of an active compound having a solubility less than 0.1 per cent by weight in water, characterized in that it contains the active compound dissolved or dispersed in a semi-solid or liquid non-ionic solubilizer selected from esters and/or ethers of polyethyleneglycols and whereby the amount by weight of the solubilizer is at least equal to the amount by weight of the active compound and that the release is controlled by a hydrophilic gel system.

2. A preparation according to claim 1, wherein the non-ionic solubilizer is selected from polyethoxylated fatty acids, hydroxylated fatty acids or fatty alcohols.

3. A preparation according to any of claims 1-2, wherein the nonionic solubilizer is selected from polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, a polyethoxylated fatty acid from castor oil or a polyethoxylated fatty acid from hydrogenated castor oil.

4. A preparation according to claim 3, wherein the non-ionic solubilizer comprises esters of hydrogenated castor oil fatty acids with oxyethylated glycerine, especially Cremophor^{R} RH 40 (BASF).

5. A preparation according to any of claims 1-4, wherein the proportions between the active compound and the solubilizer varies in the range from 1:1 to 1:10, preferably in the range from 1:2 to 1:6.

6. A preparation according to any of claims 1-5, wherein the active compound is solubilizable in the non-ionic solubilizer or in a combination of water and the non-ionic solubilizer.

7. A preparation according to any of claims 1-6, wherein the active compound comprises one or more substituted dihydropyridines.

8. A preparation according to claim 7, wherein the substituted dihydropyridine is nifedipine.

9. A preparation according to claim 7, wherein the substituted dihydropyridine is felodipine.

10. A preparation according to any of claims 1-9, wherein the hydrophilic gel-forming component constitutes between 20-80% by weight of the preparation.

11. A preparation according to any of claims 1-10, wherein the hydrophilic gel system comprises hydroxypropyl methylcellulose.

12. A preparation according to claim 11, wherein the hydroxypropyl methylcellulose has a hydroxypropyl content of 4-12% by weight.

13. A preparation according to any of claims 10-11, wherein the hydrophilic gel system contains carboxypolymethylene.

14. A process for the preparation of a solid preparation with extended release of an active compound having a solubility less than 0.1 per cent by weight in water, characterized in that the active compound is dissolved or dispersed in a semi-solid or liquid non-ionic solubilizer selected from esters and/or ethers of polyethyleneglycols in at least equal amount by weight to the active compound, whereafter the mixture is incorporated into a release controlling hydrophilic gel system and formed to a pharmaceutical dosage unit.

Claims for the following Contracting States : AT, ES, GR

1. A process for the preparation of a solid preparation with extended release of an active compound having a solubility less than 0.1 per cent by weight in water, characterized in that the active compound is dissolved or dispersed in a semi-solid or liquid non-ionic solubilizer selected from esters and/or

ethers of polyethyleneglycols in at least equal amount by weight to the active compound, whereafter the mixture is incorporated into a release controlling hydrophilic gel system and formed to a pharmaceutical dosage unit.

2. A process according to claim 1, wherein the non-ionic solubilizer is selected from polyethoxylated fatty acids, hydroxylated fatty acids or fatty alcohols.

3. A process according to any of claims 1-2, wherein the non-ionic solubilizer is selected from polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, a polyethoxylated fatty acid from castor oil or a polyethoxylated fatty acid from hydrogenated castor oil.

4. A process according to claim 3, wherein the non-ionic solubilizer comprises esters of hydrogenated castor oil fatty acids with oxyethylated glycerine, especially Cremophor^{R} RH 40 (BASF).

5. A process according to any of claims 1-4, wherein the proportions between the active compound and the solubilizer varies in the range from 1:1 to 1:10, preferably in the range from 1:2 to 1:6.

6. A process according to any of claims 1-5, wherein the active compound is sulubilizable in the non-ionic solubilizer or in a combination of water and the non-ionic solubilizer.

7. A process according to any of claims 1-6, wherein the active compound comprises one or more substituted dihydropyridines.

8. A process according to claim 7, wherein the substituted dihydropyridine is nifedipine.

9. A process according to claim 7, wherein the substituted dihydropyridine is felodipine.

10. A process according to any of claims 1-9, wherein the hydrophilic gel-forming component constitutes between 20-80% by weight of the preparation.

11. A process according to any of claims 1-10, wherein the hydrophilic gel system comprises hydroxypropyl methylcellulose.

12. A process according to claim 11, wherein the hydroxypropyl methylcellulose has a hydroxypropyl content of 4-12% by weight.

13. A process according to any of claims 10-11, wherein the hydrophilic gel system contains carboxypolymethylene.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Une préparation solide avec libération lente d'une substance active ayant une solubilité dans l'eau inférieure à 0,1 pour cent en poids, caractérisée par le fait qu'elle contient la substance active à l'état dissout ou dispersé dans un agent de solubilisation semi-solide ou liquide non-ionique sélectionné à partir des esters et/ou des éthers de polyéthylène glycol et pour laquelle la quantité en poids de solubilisateur est au moins égale à la quantité en poids de substance active et pour laquelle la libération est réglée par un système de gel hydrophile.

2. Une préparation selon la revendication 1, dans laquelle l'agent de solubilisation non-ionnique est sélectionné à partir des acides gras polyéthoxylés, des acides gras hydroxylés ou des alcools gras.

3. Une préparation selon l'une quelconque des revendications 1-2, dans laquelle l'agent de solubilisation non-ionique est sélectionné à partir de l'huile de ricin polyéthoxylée, de l'huile de ricin hydrogénée polyéthoxylée, d'un acide gras polyéthoxylé tiré de l'huile de ricin, ou d'un acide gras polyéthoxylé tiré de l'huile de ricin hydrogénée.

4. Une préparation selon la revendication 3, dans laquelle l'agent de solubilisation non-ionique conprend des esters d'acides gras d'huile de ricin hydrogénée avec de la glycérine hydroxyéthylée, en particulier le Cremophor® RH 40 (BASF).

5. Une préparation selon l'une quelconque des revendications 1-4, dans laquelle les proportions entre la substance active et l'agent de solubilisation varient dans une gamme de rapports allant de 1:1 à 1:10 de préférence dans une gamme de rapports allant de 1:2 à 1:6.

6. Une préparation selon, l'une quelconque des revendications 1-5, dans laquelle la substance active est soluble dans l'agent de solubilisation non-ionique ou dans une combinaison d'eau et de l'agent de solubilisation non-ionique.

7. Une préparation selon l'une quelconque des revendications 1-6, dans laquelle la substance active comprend une ou plusieurs dihydropyridines substituées.

8. Une préparation selon la revendication 7, dans laquelle la dihydropyridine substituée est la nifédipine.

9. Une préparation selon la revendication 7, dans laquelle la dihydropyridine substituée est la félodipine.

10. Une préparation selon l'une quelconque des revendications 1-9, dans laquelle le composé hydrophile formant un gel constitue entre 20-80% en poids de la préparation.

11. Une préparation selon l'une quelconque des revendications 1-10, dans laquelle le système de gel hydrophile comprend l'hydroxypropyl méthylcellulose.

12. Une préparation selon la revendication 11, dans laquelle l'hydroxypropyl méthylcellulose contient 4-12% en poids d'hydroxypropyle.

13. Une préparation selon l'une quelconque des revendications 1-11, dans laquelle le système de gel hydrophile contient du carboxypolyméthylène.

14. Un procédé pour l'élaboration d'une préparation solide avec libération lente d'une substance active ayant une solubilité dans l'eau inférieure à 0,1 pour cent en poids, caractérisé par le fait que la substance active est à l'état dissout ou dispersé dans un agent de solubilisation semi-solide ou liquide non-ironique sélectionné à partir des esters et/ou des éthers de polyéthylène glycol selon une quantité au moins égale en poids à celle de la substance active, après quoi le mélange est incorporé dans un système de gel hydrophile réglant la libération de la substance active puis conditionné en une unité de dosage pharmaceutique.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Un procédé pour l'élaboration d'une préparation solide avec libération lente d'une substance active ayant une solubilité dans l'eau inférieure à 0,1 pour cent en poids, caractérisé par le fait que la substance active est à l'état dissout ou dispersé dans un agent de solubilisation semi-solide ou liquide non-ionique sélectionné à partir des esters et/ou des éthers de polyéthylène glycol selon une quantité au moins égale en poids à celle de la substance active, après quoi le mélange est incorporé dans un système de gel hydrophile pour régler la libération de la substance active et conditionné en une unité de dosage pharmaceutique.

2. Un procédé salon la revendication 1, dans lequel l'agent de solubilisation non-ionique est sélectionné à partir des acides gras polyéthoxylés, des acides gras hydroxylés ou des alcools gras.

3. Un procédé selon l'une quelconque des revendications 1-2, dans lequel l'agent de solubilisation non-ionique est sélectionné à partir de l'huile de ricin polyéthoxylée, de l'huile de ricin hydrogénée polyéthoxylée, d'un acide gras polyéthoxylé tiré de l'huile de ricin, ou d'un acide gras polyéthoxylé tiré de l'huile de ricin hydrogénée.

4. Un procédé selon la revendication 3, dans lequel l'agent de solubilisation non-ionique comprend des esters d'acides gras d'huile de ricin hydrogénée avec de la glycérine hydroxyéthylée, en particulier le Cremophor® RH 40 (BASF).

5. Un procédé salon l'une quelconque des revendications 1-4, dans lequel les proportions entre la substance active et l'agent de solubilisation varient dans une gamme de rapports allant de 1:1 à 1:10, de préférence dans une gamme de rapports allant de 1:2 à 1:6.

6. Un procédé selon l'une quelconque des revendications 1-5, dans lequel la substance active est soluble dans l'agent de solubilisation non-ionique ou dans une combinaison d'eau et d'agent de solubilisation non-ionique.

7. Un procédé selon l'une quelconque des revendications 1-6, dans lequel la substance active comprend une ou plusieurs dihydropyridines substituées.

8. Un procédé selon la revendication 7, dans lequel la dihydropyridine substituée est la nifédipine.

9. Un procédé selon la revendication 7, dans lequel la dihydropyridine substituée est la félodipine.

10. Un procédé selon l'une quelconque des revendications 1-9, dans lequel le composé hydrophile formant un gel constitue entre 20-80% en poids de la préparation.

11. Un procédé selon l'une quelconque des revendications 1-10, dans lequel le système de gel hydrophile comprend l'hydroxypropyl méthylcellulose.

12. Un procédé selon la revendication 11, dans lequel l'hydroxypropyl méthylcellulose contient 4-12% en poids d'hydroxypropyle.

13. Un procédé selon l'une quelconque des revendications 1-11, dans lequel le système de gel hydrophile contient du carboxypolyméthylène.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Feststoffpräparation mit verlängerter Freisetzung einer aktiven Verbindung mit einer Löslichkeit von weniger als 0,1 Gew.-% in Wasser, dadurch gekennzeichnet, daß sie die aktive Verbindung gelöst oder dispergiert in einem halb-festen oder flüssigen nicht-ionischen Lösungsvermittler ausgewählt aus Estern und/oder Äthern von Polyäthylenglykolen enthält, wobei die Gewichtsmenge des Lösungsvermittlers mindestens gleich der Gewichtsmenge der aktiven Verbindung ist, und daß die Freisetzung von einem hydrophilen Gel-System gesteuert ist.

2. Präparation nach Anspruch 1, worin der nicht-ionische Lösungsvermittler ausgewählt ist aus polyäthoxylierten Fettsäuren, hydroxylierten Fettsäuren oder Fettalkoholen.

3. Präparation nach einem der Ansprüche 1-2, worin der nicht-ionische Lösungsvermittler ausgewählt ist aus polyäthoxyliertem Rizinusöl, polyäthoxyliertem hydriertem Rizinusöl, einer polyäthoxylierten Fettsäure von Rizinusöl oder einer polyäthoxylierten Fettsäure von hydriertem Rizinusöl.

4. Präparation nach Anspruch 3, worin der nicht-ionische Lösungsvermittler Ester von hydrierten Rizinusölfettsäuren mit oxyäthyliertem Glycerin, insbesondere Cremophor^{R} RH 40 (BASF) umfaßt.

5. Präparation nach einem der Ansprüche 1-4, worin das Verhältnis zwischen der aktiven Verbindung und dem Lösungsvermittler im Bereich von 1:1 bis 1:10, vorzugsweise im Bereich von 1:2 bis 1:6, variiert.

6. Präparation nach einem der Ansprüche 1-5, worin die aktive Verbindung im nicht-ionischen Lösungsvermittler oder in einer Kombination aus Wasser und dem nicht-ionischen Lösungsvermittler löslich ist.

7. Präparation nach einem der Ansprüche 1-6, worin die aktive Verbindung einen oder mehrere substituierte Dihydropyridine umfaßt.

8. Präparation nach Anspruch 7, worin das substituierte Dihydropyridin Nifedipin ist.

9. Präparation nach Anspruch 7, worin das substituierte Dihydropyridin Felodipin ist.

10. Präparation nach einem der Ansprüche 1-9, worin der hydrophile Gel-bildende Bestandteil zwischen 20 und 80 Gew.-% der Präparation ausmacht.

11. Präparation nach einem der Ansprüche 1-10, worin das hydrophile Gel-System Hydroxypropylmethylcellulose umfaßt.

12. Präparation nach Anspruch 11, worin die Hydroxypropylmethylcellulose einen Hydroxypropylgehalt von 4-12 Gew.-% hat.

13. Präparation nach einem der Ansprüche 10-11, worin das hydrophile Gel-System Carboxypolymethylen enthält.

14. Verfahren zur Herstellung einer Feststoffpräparation mit verlängerter Freisetzung einer aktiven Verbindung mit einer Löslichkeit von weniger als 0,1 Gew.-% in Wasser, dadurch gekennzeichnet, daß die aktive Verbindung in einem halbfesten oder flüssigen nicht-ionischen Lösungsvermittler ausgewählt aus Estern und/oder Äthern von Polyäthylenglykolen in einer mindestens gleichen Gewichtsmenge zur aktiven Verbindung gelöst oder dispergiert wird, wonach die Mischung in ein freisetzungssteuerndes hydrophiles Gel-System inkorporiert und zu einer pharmazeutischen Dosiseinheit geformt wird.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung einer Feststoffpräparation mit verlängerter Freisetzung einer aktiven Verbindung mit einer Löslichkeit von weniger als 0,1 Gew.-% in wasser, dadurch gekennzeichnet, daß die aktive Verbindung in einem halbfesten oder flüssigen nicht-ionischen Lösungsvermittler ausgewählt aus Estern und/oder Äthern von Polyäthylenglykolen in einer mindestens gleichen Gewichtsmenge zur aktiven Verbindung gelöst oder dispergiert wird, wonach die Mischung in ein freisetzungssteuerndes hydrophiles Gel-System inkorporiert und zu einer pharmazeutischen Dosiseinheit geformt wird.

2. Verfahren nach Anspruch 1, worin der nicht-ionische Lösungsvermittler ausgewählt ist aus polyäthoxylierten Fettsäuren, hydroxylierten Fettsäuren oder Fettalkoholen.

3. Verfahren nach einem der Ansprüche 1-2, worin der nichtionische Lösungsvermittler ausgewählt ist aus polyäthoxyliertem Rizinusöl, polyäthoxyliertem hydriertem Rizinusöl, einer polyäthoxylierten Fettsäure von Rizinusöl oder einer polyäthoxylierten Fettsäure von hydriertem Rizinusöl.

4. Verfahren nach Anspruch 3, worin der nicht-ionische Lösungsvermittler Ester von hydrierten Rizinusölfettsäuren mit oxyäthyliertem Glycerin, insbesondere Cremophor^{R} RH 40 (BASF) umfaßt.

5. Verfahren nach einem der Ansprüche 1-4, worin das Verhältnis zwischen der aktiven Verbindung und dem Lösungsvermittler im Bereich von 1:1 bis 1:10, vorzugsweise im Bereich von 1:2 bis 1:6, variiert.

6. Verfahren nach einem der Ansprüche 1-5, worin die aktive Verbindung im nicht-ionischen Lösungsvermittler oder in einer Kombination aus Wasser und dem nicht-ionischen Lösungsvermittler löslich ist.

7. Verfahren nach einem der Ansprüche 1-6, worin die aktive Verbindung einen oder mehrere substituierte Dihydropyridine umfaßt.

8. Verfahren nach Anspruch 7, worin das substituierte Dihydropyridin Nifedipin ist.

9. Verfahren noch Anspruch 7, worin das substituierte Dihydropyridin Felodipin ist.

10. Verfahren nach einem der Ansprüche 1-9, worin der hydrophile Gel-bildende Bestandteil zwischen 20 und 80 Gew.-% der Präparation ausmacht.

11. Verfahren nach einem der Ansprüche 1-10, worin das hydrophile Gel-System Hydroxypropylmethylcellulose umfaßt.

12. Verfahren nach Anspruch 11, worin die Hydroxypropylmethylcellulose einen Eydroxypropylgehalt von 4-12 Gew.-% hat.

13. Verfahren nach einem der Ansprüche 10-11, worin das hydrophile Gel-System Carboxypolymethylen enthält.

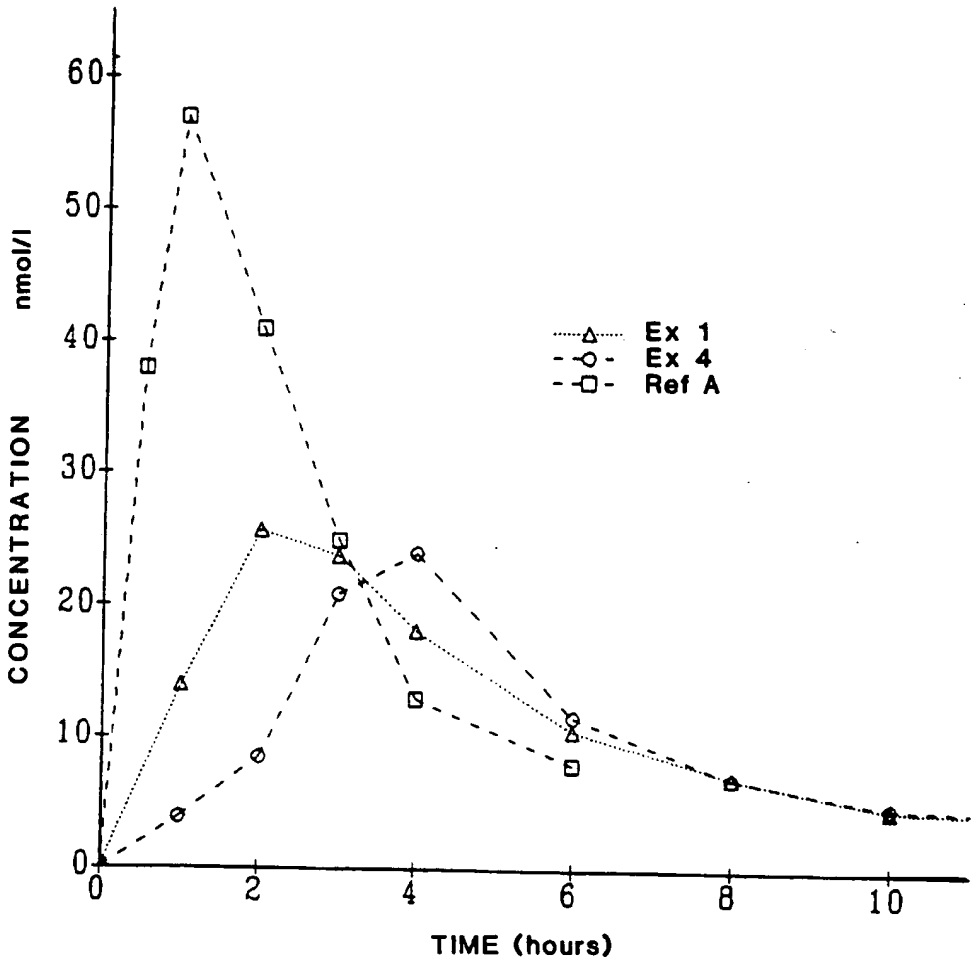
CONCENTRATION nmol/l
60
50
40
30
20
10
0
0
2
4
6
8
10
TIME (hours)
Ex 1
Ex 4
Ref A

Fig. 1

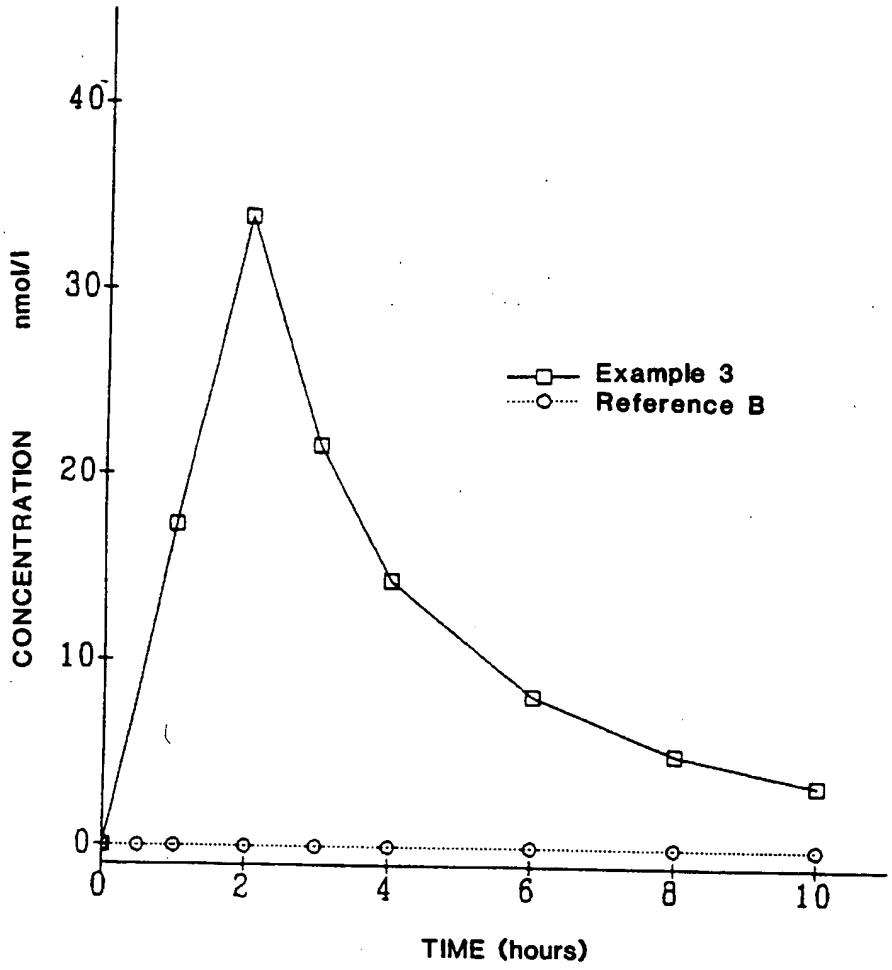
CONCENTRATION nmol/l
40
30
20
10
0
0
2
4
6
8
10
TIME (hours)
Example 3
Reference B

Fig. 2

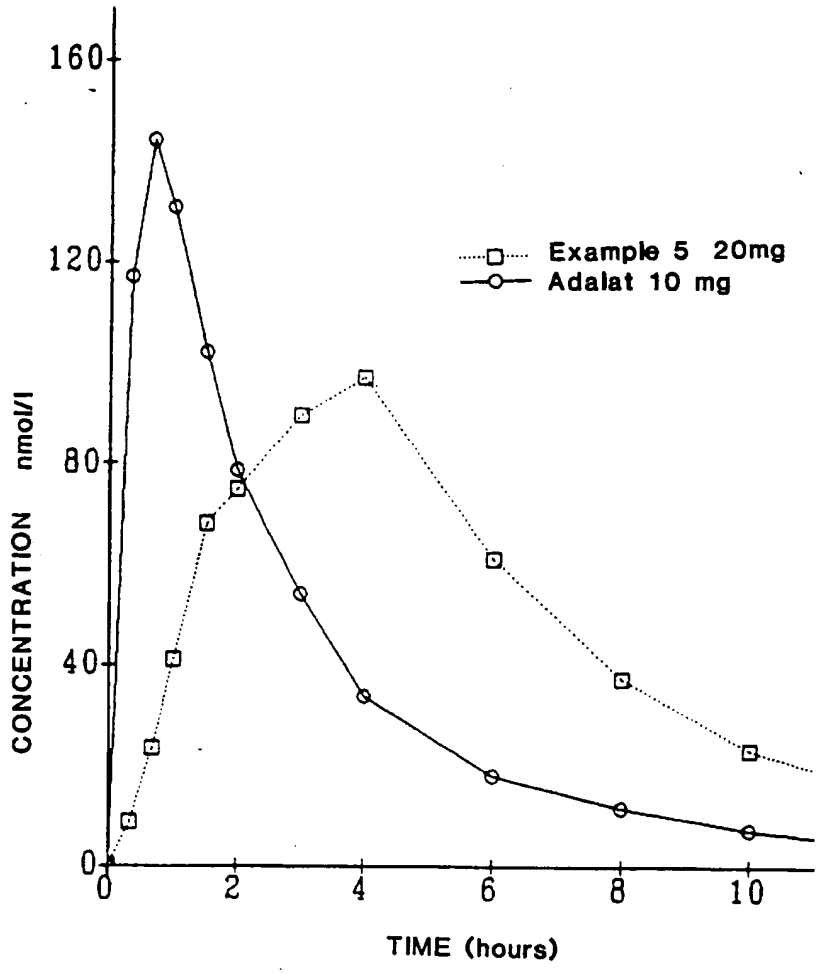
160
120
80
40
0
CONCENTRATION nmol/l
0
2
4
6
8
10
TIME (hours)
Example 5 20mg
Adalat 10 mg

Fig. 3